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A Time-Dependent Sensitization in Environmental Illness: A Pharmacologic Model @

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Time-dependent sensitization (TDS) is a well-documented process in the basic neuroscience research literature with properties that significantly overlap those of environmental illness (EI). TDS is the progressive, persistent amplification of responses within a susceptible individual from repeated, intermittent exposures to an environmental factor, pharmacological or nonpharmacological in nature. A single high dose or numerous low doses of various substances can initiate TDS, with the optimal time for testing sensitization 7-28 days after the original exposure. Multiple chemically-unrelated agents share the ability to initiate TDS; and life stress can cross-sensitize with such chemical substances. TDS has already been demonstrated with organophosphate pesticides and ethanol (a solvent) in animals. Female animals are more vulnerable than are males to TDS; estradiol accelerates the process of sensitization. Moreover, TDS can be bidirectional; the intensity of the initial exposure may determine the subsequent degree of increase or decrease in response. Responses can occur in overall behavior as well as in specific neurotransmitter, neuroendocrine, and/or immune variables. In addition, the TDS model would accommodate the observation of an apparently increased prevalence of depression, anxiety, and somatoform/post-traumatic stress-like disorder in environmentally-ill patients. TDS and its related amplification mechanism, limbic kindling, are being explored in psychiatric research as models for the long-term course of most of the above disorders. TDS research has shown that stress and chemicals cross-sensitize and that glucocorticoids accelerate acquisition of sensitization. The cross-sensitization feature of TDS predicts that demonstration of a role for one class of environmental factor (e.g., stress/depression) would actually increase, not diminish, the likelihood of a biological role for the other class (e.g., low-level chemicals). The TDS model offers a systematic, testable hypothesis to explain core aspects of EI.

GOALS AND OBJECTIVES:

The participant will be able to define time-dependent sensitization (TDS) and list its basic properties.

The participant will be able to compare and contrast the properties of TDS with those of environmental illness and of recurrent major depression.

The participant will be able to outline an experimental design to test the TDS model for environmental illness (EI) and to critique available research studies from this perspective.

OUTLINE

I. Introduction

- Review of properties of environmental illness
- Review of properties of time-dependent sensitization
- Overview of TDS model for EI

II. TDS as a model for chronic Apsychiatric@ disorders

- Recurrent major depression
- Panic disorder
- Post-traumatic stress disorder
- Illogic of concluding pschogenic etiology for EI from finding evidence of above disorders in a subset of patients
- Cross-sensitization between life stress and chemicals in TDS: How depression, if present, would increase vulnerability to low levels of chemicals on a biological basis but would not be a necessary factor in EI

III. Conclusions

- Properties of TDS overlap those of EI
- Over time, responses induced by TDS sensitizing agents become increasingly autonomous, requiring less and less of the original triggering stimulus to set off responses; thus, early intervention may be crucial to prevent chronic, treatment-resistant EI from TDS
- Testing for TDS in EI requires elimination of all cross-sensitizing factors (e.g., removing tolerance and cross-tolerance) and testing over repeated, spaced sessions under identical conditions to initiate and then assess degree of sensitization to novel substances

CONCLUSION OF WHAT IS TO BE LEARNED

Time-dependent sensitization is a well-documented process in the basic neuroscience and pharmacology literatures that offers a plausible mechanism for low-dose chemical reactivity in environmental illness. It is no longer accurate to criticize EI as a problem with Ano known mechanism@ to explain the clinical picture. Clontrary to overly simplistic interpretations of previous studies, finding psyciatric disorders in EI patients supports the TDS model and favors, rather than ruling out, chemicals as having a direct, biological role in initiating and/or perpetuating illness in EI patients.

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A**Anticarcinogenic Potential of Vitamins B_6, B_2, PP, and Methylmethionine (Vitamin U)**@

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Information about the cancer-protective effects of vitamins group B, unlike β-carotene and vitamins C and E, is limited. In experiments, we have found that vitamin B_6 (in the form of pyridoxal) and vitamin PP (in the form of nicotinamide) in relatively large doses protects from lung cancer induced in mice by procarbazine (Natulan). Dependent on dose and schedule of treatment, these vitamins decrease the yield of tumor-bearing mice by 1.5 to 4.3-fold and diminish also the number of tumors per mouse. The mechanism of these effects is under investigation. In another set of experiments, we investigated some metabolic effects of vitamin B_6 and B_2 deficiency. As it is known daughter strand of DNA, forming before cell division, needs to be methylated, and in case of undermethylated DNA forming cell has a chance to become malignant without any external carcinogenic affects. Our data reveal that alimentary vitamin B_6 and B_2 deficiency (especially if combined) produce a decreased level of tissue S-adenosylmethionine, participating in DNA methylation. So it may be suggested that under some conditions the deficiency of these factors may increase the risk of carcinogenesis. In preliminary experiments, we have found that natural sulphonium compound, methylmethionine (so-called Vitamin U) decreases sharply the yield of stomach tumors induced in rats by N-methyl-N=-nitro-N-nitrosoguanidine. In conclusion, it must be noted that separate effect of each natural compound and vitamin may be relatively weak and difficult for evaluation in humans. However, from a theoretical point of view, these effects may really exist, summarize, and potentiate each other and carcinogenic environmental factors.

AEnvironmental and Nutritional Factors of Stomach Cancer and Its Prevention@

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Stomach cancer is a widespread type of neoplasm in Russia, in regions of the former USSR, and in some countries of Europe, Asia, and Latin America. Stomach cancer incidence is associated with high content of nitrates in water and soil and with low content of ascorbic acid in gastric juice. It prevents from intragastral formation of carcinogenic nitrosocompounds from nitrates. Bacterial flora of saliva, infection of the stomach by Helicobacter pylori, and a high degree of pH of gastric juice may further the conversion of nitrates to nitrites and nitrosocompounds. Among risk factors of stomach cancer, there are atrophic gastritis, preceding partial resection of stomach and affecting some promoters (NaC1 and bile). In the case of atrophic gastritis, relatively low doses of radiation sharply increase the risk of stomach cancer in experiments. Taking into account how widespread atrophic gastritis is among the people in Russia, Belarus, and the Ukraine following their exposure to radiation as a result of the Chernobyl disaster, we suggest that the rate of gastic cancer in these regions in recent years will increase.

High risk of stomach cancer is correlated also with low consumption of β-carotene (β-C). In our study, we found that β-C given daily in a dose of 10-20 mg produces in the stomach mucosa of patients with atrophic gastritis a significant decrease in abnormally high activity of ornithine decarboxylase (ODC), which serves as a marker of tumor promotion. Blocking of ODC can prevent the incidence of cancer in experiments and probably can delay the theoretical time of tumor appearance in humans over the natural-limited period of life.

OUTLINE

The goal of my two talks is to attract the attention to new data concerning anticarcinogenic activity of β-carotene and some other vitamins that may increase the resistance of organism to injurious factors of environment.

Our data reveals that some vitamin B groups (B_6, B_2, PP) and methylmethionine can block chemical carcinogenesis or prevent from undermethylated DNA. On the other hand, we have found that β-carotene and to some degree vitamin E can block the promotion stage of carcinogenesis in patients with an increased risk of gastric cancer.

Decrease in risk of cancer incidence as a result of possible vitamin action must be evaluated in clinical and epidemiological interventional studies.

Partially the results obtained were published in the following:

Bukin, Yu V., et al. 1989. Problems of oncology (Russian, English abstr.) 35:34-38.

Bukin, Yu V., et al. 1991. First Int. Congress on AVitamins and Biofactors in Life Science@ (abstracts, p. 70). Kobe Japan.

Bukin, Yu V., et al. 1993. *Europ J Cancer Prev*. (1): np.

AFungal/Mycotoxin Etiology of Gout and Hyperuricemia@

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Gout and hyperuricemia are clinical entities of previously unknown etiology. Fungi/mycotoxins have been ignored as the documented cause of both entities. The etiopathogenetic mechanisms are not the usual patterns of invasive-type mycoses nor of mycotoxicoses, but incorporate occult features of both of these mechanisms resulting in abnormal biochemical findings associated with specific granuloma tissue lesions. All of the biochemical findings in gout/hyperuricemia are explainable by fungal production of preformed urates/urate crystals, oxalate, glutamate, glycosaminoglycan, glycoprotein, and hormones. Mycotoxins cause hyperuricemia and hyperlipidemia. The gouty tophaceous lesion is a granuloma of the delayed hypersensitivity type and is identical to fungal granulomas. Asteroid bodies, characteristic of fungal lesions, are found in the giant cells in both avian and human gouty tophi. Asteroids are fungal cells coated with fungal antigen+host antibody. Spherules and branching filaments present in tophi have been misidentified as urates on silver stain which also stains fungal forms the same identical color. Periodic acid Schiff stain has demonstrated faint-staining fungal spherules in gouty lesions. The clinical course of an acute attack of gout is that of a fungal infection with prodrome, all the usual signs of infection, ascending

lymphangitis, fever, chills, increase in sedimentation rate, and desquamation of the overlying skin. Gout responds to the same mode of action as colchincin. These clues led to the observation that all drugs and dietary factors improving gout/hyperuricemia possess antifungal and/or antimycotoxin activity. The fungal etiology of gout/hyperuricemia provides a rational basis for preventive measures and correct therapy.

A**The Fungal/Mycotoxin Etiology of Atherosclerosis and Hyperlipidemia**@

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Atherosclerosis and hyperlipidemia are clinical entities of previously unknown etiology. Fungi and their toxins have been ignored as documented etiology of both entities. Hyperlipidemia is induced by a number of mycotoxins. Seasonal variations in hyperlipidemia correlate to seasons of maximal fungal growth and mycotoxin production. It will be shown in this presentation that hyperlipidemia is a protective-toxin binding mechanism that is seen in a number of complex infections and it returns to normal with antibiotic therapy and/or toxin bind-agents, including charcoal. Atherosclerotic lesions are characterized by lipid deposition, foam cells, endothelial cell damage, smooth muscle cell proliferation, activation of all of the cellular and humoral elements of delayed hypersensitivity, and fibrosis/calcifications. All of these lesions are induced in animals and humans by fungi/mycotoxins. Cyclosporine, a mycotoxin (an immuno-toxic fungal antibiotic), causes accelerated atherosclerosis and hyperlipidemia in the vast majority of transplant patients. Primates developed hyperlipidemia and atherosclerosis when fed Fusarium toxins (corn). Hyperlipidemia associated with lipid-containing vascular lesions is found in sheep ingesting the mycotoxin sporidesmin. In humans, ergots induce spasm, stenosis, and/or thrombosis of the coronary, carotid, aortic, renal, and peripheral arteries. Ergot-induced entities include angina, myocardial infarctions, arrhythmia, carotid artery occlusion, stroke, intermittent claudication and gangrene. All drugs and dietary measures effective in treating atherosclerosis and/or hyperlipidemia share only antifungal or antitoxicity activity (lovastatin, griseofulvin, ketoconazole, neomycin, fibrates, etc.).

Auto-immune diseases are characterized by the finding of so-called auto-antibodies. It is a most popular concept but biologically fatally defective in that no species of life can make an antibody against itself, particularly, causing fatal disease such as scleroderma. Scleroderma is considered to proved the validity of the auto-immune concept with the presence of auto-antibodies against ubiquitin, which is present in many species including fungi. Scleroderma responds well to the antifungal agent griseofuvlin. Against whose ubiquitin is the host raising antibodies to its own or fungal-derived in a disease state that responds to an antifungal drug? The auto-immune diseases appearin gto have a fungal/mycotoxin origin are scleroderma diabetes mellitus, HLA-related disease, rheumatoid arthritis, Sjogren-s syndrome, psoriasis, and systemic lupus erythematosus. All of the drugs effective in the treatment of these diseases possess antifungal or anti-mycotoxin activity. This includes all NSAIDS.

GOALS AND OBJECTIVES:

The purpose of presenting the three papers relative to the role of fungi/mycotoxins in the etiology of atherosclerosis/hyperlipidemia, gout/hyperuricemia, and auto-immune diseases and malignancies is to

introduce the medical and medical-allied profession to a rapidly evolving data base documenting this etiological relationship.

The Surgeon General has indicated that the leading nine causes of death (and morbidity) are all diet-related. Yet commonly consumed natural food is not poisonous, per seCa fact adequately supported by the lack of published data that natural food itself is toxic.

It is not the food itself but the mycotoxins present on the foodCparticularly those stored and/or fermented by fungiCthat are injurious to one=s health.

Animal fat is dangerous in that it contains sequestered/stored mycotoxins.

Tobacco is actually a fermented leaf that contains fungi plus a significant amount of known cancer-producing and atherosclerosis-producing mycotoxins. Passive smoking is causing disease because the smoke particles are coated with mycotoxins.

Even yeast-fermented bread falls outside the definition of natural food, which probably accounts for its recent documentation as an etiological agent of breast cancer in Japan.

The same yeast used to leaven bread caused severe lipid vascular deposits in ratsCthe pattern mimicking human vascular lipid deposits.

Beer causes cancer of the kidney and breast.

CONCLUSION OF WHAT IS TO BE LEARNED

The dietary connection to environmental health is increasingly being made clear in that the causation of the major diseases related to diet are not due to the food but rather to the fungi and mycotoxins present in the food chain.

While manmade chemicals used in agriculture, industry and homes, also play a role in human health the data supporting a fungal/mycotoxin etiology of each of the major diseases is overwhelming while manmade toxicity studies do not show a similar connection to these diseases.

However, the two types of environmnetal toxic exposures do come together at various junctions, such as the increased incidence of gout and hypertension in persons exposed to lead; the lead injuries the immune system, which predisposes the person to increased risk of infections, in general, and, more specifically, in host fungal colonization/toxin production. On the other hand, the extensive use of antifungal agents to limit mycotoxin production in stored grains over the past three decades has probably resulted in the side benefit of a 50% reduction in heart attacks and gastric cancer over the same period of time.

A**Some Thoughts on Chemical Sensitivity**@

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Individual sensitivity to environmental chemicals is divided into two groups. Classical allergies are mediated through the immune system usually due to IgE. Chemical sensitivities are usually caused by genetically impaired enzyme systems and are often precipitated by heavy chemical exposures.

Chemical sensitivity is often a multisystem disorder with a large number of symptoms including profound lethargy, headache, irritable bowel syndrome, skin rashes and eczema, joint pains, numbness of the extremities, and temperature sensitivity. There is often a family history together with a major chemical exposure. An example will be given of a complex case related to exposure to the fumes of absolute alcohol used as a biological preservative. Analgesic inudced headache is caused by up-regulation of prostaglandins following prolonged used of analgesics to control headaches. The condition only occurs in sensitive individuals with pre-existing headaches such as migraine. Withdrawal of analgesics leads to significant improvement in 80% of patients. Migraine affects 10% of the population, and hence this is both a simple and an important form of chemical sensitivity.

Glue sniffing is a common form ofsolvent abuse in adolescents and is occasionally associated with sudden death caused by a solvent-induced arrhythmia. Myocardial sensitivity to solvents and aerosol propellants is potentially serious, particularly when combined with anoxia. Chemical sensitivity should be considered in patients with cardiac arrhythmia when there is no obvious underlying cardiac pathology. It is concluded that there are many different types of chemical sensitivity and that they are of importance in clinical medicine.

OUTLINE

Goals and Objectives:

To illustrate the importance of chemical sensitivity in clinical medicine.

Conclusions of what is to be learned:

The examples given in the talk should emphasize the importance of chemical sensitivity in medical practice.

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A**Toxicity of Heated Food in Relation to Cooking Temperature**@

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It has been widely demonstrated that current cooking practices, such as frying, broiling, and baking, induce the formation of heterocyclic amines in food.

The Ames/Salmonella test has shown that these compounds have a significant mutagenic activity. Interesst in these substances was increased by their carcinogenicity in rodents. Furthermore, microsomal fractions of human liver convert heterocyclic aromatic amines to potent mutagens in the Ames test and certain amines were found in human urine, bile, liver, and kidney. This indicates that those compounds that are consumed daily could be possible human carcinogens.

Nevertheless, the toxicological consequences have not so far been clearly demonstrated but are suspected to play a part in the etiology of a large number of diseases.

For this reason, we have been investigating methods to reduce or eliminate the compounds from our diets by reducing the cooking temperature and by eliminating certain cooking methods requiring high temperatures.

This conclusion is the result of a bibliographic study. It is based on a significant number of converging facts that are worrisome. These have led us to define an attitude of caution before further experiments are

carried out.

OUTLINE

Goals and objectives:

Our goal is to realize a synthesis of scientific publications on the subject of heated food toxicity. More generally, we want help physicians, food producers, and the public become sensible to the toxicity of heated food at high temperature.

Outline of talk/abstract:

This article is the first of a series. It concerns mutgenicity and carcinogenicity of Heterocyclic Amines (Has) because today they seem to be some of the most important hazardous substances appearing when we heat food at usual temperature in household cooking or industrial food processing.

Conclusion of what is to be learned:

We believe that it is not reasonable to wait for decisive proof to reduce our cooking temperature to values below 150EC, ideally at 100E C.

AEffects of Mycotoxins on T4 Lymphocytes@

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Aflatoxins B_1, B_2, G_1, and G_2 were observed to be mitogenic to human peripheral T_4 lymphocytes by using the techniques of flow cytometry. Lymphoctyes were obtained by venipuncture and propagated in RPMI 1640 medium, stained with propidium iodide and fluorescein isothiocyanate (FITC), and examined microfluorometrically. Blastogenesis was observed as a measure of the rapid and stoichiometric binding of a fluorochrome to the DNA of each lymphocyte and examining the fluorescence of each cell. All the aflatoxins used were found to be mitogenic, and resolution of lymphocytes was observed prinicapally in the G_2/M growth cycle.

OUTLINE

Goals and objectives:

To determine, by the use of flow cytometry, whether or not aflatoxins B_1, B_2, G_1, G_2 would stimulate blastogenic response to human peripheral T_4 lymphocytes and to determine on the basis of DNA content,

the percentage of cells from a specific number that was stimulated in each growth cell.

Conclusion of what is to be learned:

Showed that aflatoxins are mitogenic to T_4 human peripheral lymphocytes; and that the degree of stimulation is directly related to concentration. Aflatoxins B_1 and B_2 appeared to be more mitogenic than G_1 and G_2. In all cases, the principal mitogenic response was observed in the G_2/M growth cycle according to the DNA profile.

This investigation provides the following:

1. A rapid and highly reproducible method for assessing the mitogenicity of various substances and the classification and resolution of lymphocytes that are stimulated.

2. An opportunity for a more efficient investigation and treatment of individuals who are exposed to aflatoxins and other substances that are mitogenic to T_4 lymphocytes and who are manifesting symptoms related to T_4 lymphocyte deficiencies.

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A**Health Implications of Pre- and Post-natal Aflatoxin Exposure**@

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During the last trimester of pregnancy, 10-25% of Nigerian and 18-28% of Zambian women had serum aflatoxins at levels ranging from 10 to 43,489 pg/ml at various times. At birth, 14% of Nigerian and 28% of Zambian mothers had aflatoxins in their blood. Mean levels were 3,157 and 10,096 pg/ml, respectively. There were aflatoxins in 16% of Nigerian and in 25% of Zambian cord bloods. Mean levels were 2,942 and 8,210 pg/ml, respectively. The highest level was 108,625 pg/ml in a Zambian infant. About 30% of all breast milks analyzed in both countries showed aflatoxins in amounts up to 49,225 pg/ml. All infants exposed to aflatoxin blood levels >1,000 pg/ml pre-natally, followed by exposure to breast milk aflatoxins >100 pg/ml, were reported to be unwell at ALL visits to the clinic. Analysis of organs from autopsies on an unexplained stillbirth and an early neonatal death of obscure cause revealed significant amounts of aflatoxins in organs from both. Aflatoxins were implicated in the pathogenesis of Aunexplained@ neonatal jaundice in G6PD-normal infants in Nigeria.

OUTLINE

Goals and objectives:

Studies have been undertaken to determine the frequency and severity of fetal aflatoxin exposure during pregnancy and during lactation in areas where aflatoxin contamination of human diets is common, and attempts have been made to correlate these observations with neonatal health and survival.

Outline of talk/abstract:

Findings in pregnancy, at delivery, and during the neonatal period recorded in Zambia and Nigeria on mothers and babies show that in these countries pre-natal and post-natal aflatoxin exposure occurs commonly and is often severe. Such exposure is associated with ill health in the newborn period and may cause stillbirths and early neonatal death.

Conclusion of what is to be learned:

Aflatoxins have not previously been shown to constitute a risk factor to mothers and babies during pregnancy. These findings open up a vast new area for clinical-biochemical-pathological exploration.

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A**The Hypothesis that Incriminates Aflatoxins in Kwashiorkor**@

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Kwashiorkor is a disease of obscure etiology characterized by edema and low serum proteins, variable skin and hair changes, apathy and peevish irritability, immunosuppression, and a variety of biochemical disturbances. The concept that it is due to protein malnutrition is no longer tenable.

The geographical and seasonal predilections of aflatoxins andd kwashiorkor are remarkably similar as are the biochemical and immunological derangements caused by aflatoxins in farm and laboratory animals and those observed in children with kwashiorkor.

Recent controlled studies have shown the following:

1. Aflatoxins occur in kwashiorkor sera in higher concentrations and more frequently than in normal or marasmic children.

2. Aflatoxicol occurs frequently in kwashiorkor sera but never in normal or marasmic children.

3. Autopsy livers from 57 kwashiorkors contained aflatoxins which were not found in any controls.

4. Many foods and human breast milk contain aflatoxins in kwashiorkor endemic areas.

5. The transformation of AFB1 to less-toxic derivatives and urinary excretion of aflatoxins are impaired in kwashiorkor.

The aflatoxin hypothesis provides rational explanations for all the peculiarities of kwashiorkor that have defied explanation for 60 years.

OUTLINE

Goals and objectives:

The etiology of kwashiorkor, which causes much sickness and death in the tropics, remains obscure. Establishing a link with aflatoxins will provide a rational approach to prevention and management of the disease.

Outline of talk/abstract:

Results of studies undertaken in several countries in tropical Africa have established firm associations between aflatoxins and kwashiorkor. Proof that this association is causal has yet to be firmly established.

Conclusion of what is to be learned:

Epidemiology, clinical manifestations and biochemical and immunological derangements in Kwashiorkor: The seasonal and geographical exposure of children to aflatoxins and the effect of these toxins on nutrition, biochemistry, and immunity and evidence from field and laboratory studies that link kwashiorkor and aflatoxins.

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A**There=s No Place Like Home**@

Geoffrey H. Hutton, Dip. Arch.

Hutton + Rostron

Gomshall, Surrey, Eng.

Geoffrey Hutton, an architect concerned with building research and information, deals with buildings and changing lifestyles as vectors in illness, particularly in allergic conditions, and the agents in the construction and use of a building that can predispose to such conditions, for example, moisture, dust, volatiles, and biological influences. Areas of concern in an environmental assessment of a building are dealt with such as the physical construction, services and utilities, location, occupancy, furnishings, consumables, and maintenance. The speaker argues that the building should be considered as part of a whole diagnosis and that the home as much as the place of work can produce a combination of agents and circumstances, including stress, which can reinforce, if not be the direct cause of, a perceived illness. The

speaker concludes that the home as well as the workplace should be included in an assessment of the causation of illness and that building design and construction should be modified in the light of this experience. To this end, an integration of the data derived from clinical case notes, the environment, occupation, social circumstances, and buildings is proposed as a master list for comparative studies, epidemiology, and environmental assessment.

OUTLINE

Goals and objectives:

To draw attention to the changes in building construction and occupancy that have consequences for health.

Conclusion of what is to be learned:

The home as well as the workplace should be included in an assessment of the causation of illness and that building design and construction should be modified in the light of this experience.

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Allergy Problems in Buildings, The proceedings of a conference in June 1992 at the Royal Society of Arts, London; to be published by Quay Publishing.

A**Pupillary Response in Chemically Sensitive Patients**@

Satoshi Ishikawa, MD, Yutaka Masuda, MD, and Tatsuto Namba, MD

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Pupil responses to the light can express the change in the autonomic nervous system. We have examined the responses using infrared video-pupillography (Iriscorder-Hamamatsu C-2515 and 2514) with a total of 1001 patients who visited the Environmental Health Center-Dallas during 1989-1992. The patients were diagnosed as chemically sensitive in most of the cases.

The pupillary responses were analyzed, and the following results were obtained: the normal responseC41.5%; inhibited sympathetic nervous systemC26.2%; excited sympathetic nervous systemC1.4%; excited parasympathetic nervous systemC24.3%; and inhibited parasympathetic nervous systemC4.3%.

The pupil system may be helpful for quantification of an impairment of the autonomic nervous system in the patients with chemical sensitivity and may be usable as the noninvasive screening method for test subjects.

In addition to the above results, our recent finding on the pupil research will be included.

OUTLINE

Goals and objectives:

An objective method of the finding to establish the diagnosis in patients with environmentally induced Achemical sensitivity.@ The author used pupillary responses to the light stimulus and analyzed the dynamics of constriction and dilatation of the pupil.

Outline of talk/abstract:

The author will present the results of pupil analysis in patients who visited the Environmental Health Center-Dallas under the diagnosis of chemical sensitivity during the past two years (N=100 cases). Normal response was found in 41.5% of the total cases. The others had more or less abnormal function in the autonomic nervous system.

Conclusion of what is to be learned:

The pupil system may be helpful for quantification of an impairment of autonomic nervous system in the patients with chemical sensitivity and may be able to use the technique for the screening of those cases.

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AOsteopathic Approach to Autonomic Nervous System Dysfunction@

Alfred R. Johnson, DO

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Osteopathic manipulative techniques have been used since the late 1800s in the treatment of somatic and visceral dysfunctions. Basic principles will be discussed with special attention to the normalization of the autonomic nervous system via the feedback loop mechanisms. Diagnostic test through palpatory skills are essential in evaluating the individual. The somatic visceral relationships will also be discussed in detail to help the participant understand specific areas of palpatory changes in the relationship to the organ dysfunction.

OUTLINE

Goals and objectives:

To acquaint the symposium participants with the basic osteopathic concepts, their use and their use in somatic dysfunction and disease processes.

Conclusion of what is to be learned:

The participant will become more familiar with the osteopathic technique and how it may help their individual patients.

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A**The Alphabet Soup of Chemical Sensitivity**C**MCS, SBS, RADS, AND RUDS**@

William J. Meggs, MD, PhD

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Greenville, North Carolina

As interest in sensitivity to environmental chemicals has broadened, a number of chemical sensitivity syndromes have been described. Unfortunately, the confusion and controversy surrounding chemical sensitivity continues to expand and probably will not resolve until the mechanisms behind these syndromes are demonstrated. The Sick Building Syndrome (SBS) is a term to designate an outbreak of

illness associated with indoor air contaminants in new and tightly sealed buildings. Symptoms include irritation of the eyes, nose, and throat, skin irritation, and neurotoxic symptoms, including mental fatigue and difficulty with concentration. The syndrome is an acquired disorder with onset related to moving into a new or renovated building, and there is wide individual variability in onset and symptoms following a given exposure.

The multiple chemical sensitivity syndrome (MCS) begins with an environmental exposure, most commonly a solvent or pesticide. After the initial exposure, individuals become sensitive to low-level chemical exposures with symptoms involving more than one organ system. Though this syndrome was described four decades ago, it remains highly controlversial.

The reactive airways dysfunction syndrome (RADS) is an asthma-like illness that develops within minutes to hours following an acute exposure to a dust, smoke, or solvent. There is persistent bronchial hyperreactivity with positive methalcholine challenge. The asthma becomes chronic after the initial exposure and can be difficult to treat. The reactive upper-airways dysfunction syndrome (RUDS) also follows a chemical exposure, and there is a persistent chronic rhinitis. The chief complaint of patients with RUDS is chemical sensitivity. Unlike patients with RADS, medical attention is not sought on the day of exposure, which probably reflects the fact that breathing is compromised in RADS but not in RUDS. Lymphocytic infiltrates are seen on nasal biopsy. Electron microscopy has shown thickening of the basement membrane and desquamation of the respiratory epithelium.

There are many similarities between SBS, MCS, RADS, and RUDS, and these syndromes may all be manifestations of neurogenic inflammation.

A**Neurogenic Inflammation and Chemical Irritant Receptors**@

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Complaints of sensitivity to environmental chemicals are numerous, and a number of clinical syndromes have been defined as clinical entities in which exposure to chemical inhalants gives rise to disease. These include the sick building syndrome, environmental illness, and the multiple chemical sensitivity syndrome. These syndromes have generated great controversy, with a division of opinion between those who feel that these are psychological disorders versus those who believe that there is a physiological basis to these disorders. Resolution of the controversy surrounding these syndromes will most likely require an understanding of the mechanisms by which environmental exposures can trigger illness. Evidence for neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation is reviewed, and the role of neurogenic inflammation in disorders such as asthma, migraine headache, arthritis, and contact dermatitis is discussed. Current data on the existence of chemical irritant receptors in the airway and skin are discussed, and neurogenic inflammation arising from stimulation of chemical irritant receptors is found to be a remarkable model to explain many of the aspects of chemical sensitivities. Current thinking on the regulation of neurogenic inflammation suggests mechanisms

by which an acute chemical exposure can trigger chronic chemical sensitivity, which is an invariable feature of chemical sensitivity syndromes. Establishing a link between neurogenic inflammation arising from chronic stimulation of chemical irritant receptors and clinical syndromes related to environmental chemicals should be a research priority.

AA Limbic System Model for Multiple Chemical Sensitivities@

Claudia S. Miller, MD

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San Antonio, TX

Sensitivity to low-level chemical exposures is of increasing concern to patients, physicians, and regulatory agencies, among others. The hypothesis is presented that a primary mechanism for chemical sensitivity may involve the central nervous system, in particular, the limbic system, which may secondarily affect the immune system and other organ systems in a variety of ways. Adaptation and the overlapping effects of everyday exposures may make it necessary to place patients who report chemical sensitivities in a controlled environment for extended periods prior to provocative challenges. Cacosmia (feeling ill from odors) may affect one-third or more of the the general population. Multiple chemical sensitivity (MCS) patients represent a tiny fraction of cacosmics, but both groups may experience cognitive impairment and other adverse effects with exposure to low levels of volatile organic compounds (LLVOCs).

OUTLINE

Goals and objectives:

1. To define for participants the potential role of the limbic system in chemical sensitivity.

2. To delineate the interrelationship between adaptation and chemical sensitivity.

3. To outline for participants possible future directions for research on chemical sensitivity.

Outline of talk/abstract:

I. Introduction

II. Clinical observations on MCS

III. The limbic system

IV. Adaptation

V. Conclusion

Conclusion of what is to be learned:

At the conclusion of the presentation, participants should understand and be able to describe the following:

1. The physiological and psychological functions that are influenced by the limbic region and how the limbic system may be affected by chemical exposures.

2. The role of adaptation in human responses to a wide range of environmental chemical exposures and the purpose of using an environmentally controlled facility for studies of such responses.

3. The possible relationships between olfactory-limbic function, adaptation, and chemical sensitivity.

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A**Mycotoxins in Blood and Air**@

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Those of us working in environmental medicine are well aware of the long-term effects of low-level exposure to chemicals such as formaldehyde, or solvents, whereas the majority of toxicologists are particularly concerned with gross effects of immediate exposure.

Similarly, one must be aware of long-term, low-level effects of exposure to mycotoxins engendering

chronic disease, rather than the acute exposure to large quantities of the fungal poisons. This difference between acute and chronic exposure can only be learned from the effects of acute exposure in the first instance. Acute toxicological effects are easier to identify and quantify than possible long-term consequences.

A**Toxic Metabolites of Molds**C**Diversity of Biological Activity**@

Maurice O. Moss, PhD

University of Surrey

Guildford, Eng.

A consequence of the diversity of chemical structure of mycotoxins is the wide range of biological activity associated with them. Thus, the aflatoxins are both carcinogenic and acutely hepatotosic, the ochratoxins are nephrotoxic, and the trichothecenes are acute cellular toxins. All three groups are also immunosuppressive, an activity possibly mediated by the different ways in which each inhibits protein biosynthesis.

In some cases, such as the aflatoxins, toxicity expressed is the outcome of the bodies own metabolic activity, i.e., the metabolites produced by the fungi are required to be activated in some way. In other cases, such as the trichothecenes, the metabolites produced by the fungi are almost certainly the active toxins. The need for activation of mycotoxins such as aflatoxin B_1 accounts for the large diversity in activity among different species and, indeed, between the sexes of the same species. In contrast, the toxicity of a trichothecene such as T-2 toxin is very similar, irrespective of species or sex.

OUTLINE

Goals and objectives:

To demonstrate the diverse mechanisms by which mycotoxins have a biological effect and to show the possibility for interactions between them.

Outline of talk/abstract:

Known are mycotoxins that are carcinogenic, nephrotoxic, and hepatotoxic. Also known are mycoyoxins that affect various aspects of nerve action, have dermal activity or are acute cellular toxins. Some mycotoxins need to be metabolized before becoming toxin; others are almost certainly toxic in their natural state. This diversity of toxic potential makes it probable that combinations of several mycotoxins may act synergistically. Some are immunosuppressive.

Conclusion of what is to be learned:

That the biological activity of mycotoxins may account for some aspects of ill health in humans.

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A**Toxic Metabolites of Molds and Algae**C**An Overview**

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Many species of filamentous fungi can produce toxic metabolites known as mycotoxins. Both freshwater and marine species of algae are also capable of producing complex toxic metabolites. Although there are clear patterns in the biosynthetic pathways leading to the production of these metabolites, the diversity of chemical structures is enormous. Many of them, such as the aflatoxins, the trichothecenes, and the ergot alkaloids, are produced as families of compounds. The major significance of the mycotoxins is their possible occurrence in foods and animal feeds following invasion of these commodities by molds. It is also possible for them to pass through a food chain contaminating a commodity such as milk, which has not itself been attacked by mold. Algeal toxins are also usually passed through a food chain via other animal species, such as shellfish.

Although algeal and fungal toxins have received most attention as food associated problems, it is possible that they may also occur in other aspects of the human environment such as the water we drink, tthe air we breathe, or the materials we touch.

OUTLINE

Goals and objectives:

To provide an overview of the diversity of structure of the toxic metabolites produced by a diverse range of fungi and algae and to review their significance in human health.

Outline of talk/abstract:

Many species of filamentous fungi can produce toxic secondary metabolites known as mycotoxins. The

major significance of these is their occurrence in foods and animal feeds following mold invasion of these commodities. There are, however, other situations in which these toxic compounds may occur in the human environment. Equally, both marine and fresh water algae can produce a diverse range of complex toxic metabolites, some of which also find their way into the human food chain through absorption and concentration in other animals such as shellfish.

Conclusion of what is to be learned:

That fungi and algae are sources of complex chemical structures many of which show biological activity.

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A**Fumonisin Mycotoxins in Animal and Human Diseases**@

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Richard B. Russell

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Fusarium moniliforme Sheldon is a common mold contaminant of corn and is found throughout the world wherever corn is grown. Contamination of food with the fungus has historically been associated with several animal diseases, including equine leucoencephalomalacia (ELEM) and porcine pulmonary edema (PPE). There is also epidemiological evidence that high rates of esophageal cancer occur in certain populations that consume large amounts of F. Moniliforme-contaminated corn. The fumonisins are a recently discovered group of mycotoxins produced by F. Moniliforme. The following topics relative to the role of fumonisins in animal and human health will be discussed. (1) Administration of purified fumonisin B_1 (FB_1) produced ELEM in horses and PPE in pigs. FB_1 causes hepatotoxicity and nephrotoxicity in rats, and when fed to rats in long-term studies, it causes hepatocellular carcinoma. (2) The mechanism of fumonisin toxicity appears to be the result of inhibition of sphingolipid metabolism. Sphingosine, sphinganine, ceramides, and glycospingolipids are important components of all cells, and they serve both structural and functional purposes. Interference with regulatory and second messenger activities of sphingoid bases by fumonsisins could result in a number of adverse responses including cell death, altered

metabolic pathways, and proliferation of initiated cells through deregulation of protein kinase C. (3) Distribution studies of radiolabelled FB_1 indicated that the toxin is poorly absorbed from the gastrointestinal tract, but once absorbed, it appears to persist in target tissues. (4) The extent to which fumonisins and fumonisin-like compounds contaminate our food and feed supply and the effects of long-term, low-dose consumption of the toxins needs to be determined.

OUTLINE

Goals and objectives:

To review the role of the fungus Fusarium moniliforme and one of its mycotoxins, fumonisin B_1, in animal and human health problems.

Outline of talk/abstract:

I. Introduction

II. Disease associated with F. moniliforme and fumonisins

A. Equine leucoencephalomalacia

B. Porcine pulmonary edema

C. Human esophageal cancer

III. Mechanism of fumonisin toxicity

A. Effect of fumonisins on sphingolipid metabolism

B. Implications for altered sphingolipid metabolism

IV. Distribution and toxicokinetics of fumonisin B_1

V. Summary and conclusions

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A**The Scope of Mold Sensitivities in Children**C**Practical Clinical Aspects**@

Doris J. Rapp, MD

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Buffalo, New York

This presentation includes physical, behavioral, and learning problems due to molds and yeast in sensitive infants and children. When and how to suspect and confirm the etiology of mold-related problems will be discussed. Therapeutic and testing challenges with suggestions about how to handle these in infants and children will be presented.

Case Histories:

1. A 3-month infantCextensive diaper rash not helped by 23 MDs, improved in office hours, 50% better in 13 hrs and 85% in two days.

2. Sleeping infant bit off end of tongue. Incisors removed. Bit tongue sides. With mold P/N test, slept, bit, and had bloody saliva. Mold extract relieved problem.

3. A 15-year-old female, head and eye aches when outside her cheese-smelling town. Double-blind allergy extract prepared from the outside air precipitated and eliminated the headaches.

Video Presentation:

Children aged 6-16 years reacting to mold testing and therapy with anger, depression, irritability, biting, punching, slapping, extreme fatigue, silliness, hyperactivity, reluctance to be touched, and/or inability to write and learn.

OUTLINE

Goals and objectives:

To give an overview of certain practical aspects about the expansive role of mold sensitivities in infants, children, and adults.

Conclusion of what is to be learned:

How to recognize, diagnose, and treat the many forms of mold sensitivities in infants, children, and adults.

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A**The Evaluation of the Autonomic Nervous System in Chemical Sensitivities**@

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The chemically sensitive patient has many symptoms that are explained by triggering of the autonomic nervous system. New technology using the Iriscorder has allowed us to measure the sypathomimetic, sympatholytic, cholinergic, and cholinolytic in over 1,000 patients. The predominant findings are cholinergic and sympatholytic effects.

A study was done using 44 chemically sensitive patients to see if inhalant challenge of ambient doses of chemicals can change pupil relexes. The challneges of organophosphorus pesticide, toluene, phenol, and chlorine produced statistically significant differences in pupil function. Organophosphorus pesticide stimulates cholinergic nerve, while toluene inhibits the sympathetic nerve, and phenol produces sympathetic nerve excitation or cholinergic nerve inhibition, after low levels of exposure.

OUTLINE

Goals and objectives:

Functions of the autonomic nervous sytemChow to measure it. Symptoms related to chemical sensitivity.

Outline of talk/abstract:

A. General autonomic functionsCsympatholytic, sympathomimetic, cholinergic, cholinolytic

B. Challenge testsCchanges at the above

Conclusions of what is to be learned:

Autonomic nervous system is dysfunctional in the chemically sensitive

REFERENCES

S. Shirakawa, W.J. Rea, S. Ishikawa , and A.R. Johnson. Evaluation of the autonomic nervous system response by pupillographical study in the chemically senstive patient. *Environmental Medicine* 8(4):

A**The Effects of Mycotoxins on Chemical Sensitivity**@

William J. Rea, MD

Environmental Health Center-Dallas

Dallas, TX

It is clear the mycotoxins do influence total body load. The extent to which mycotoxins disrupt the chemically sensitive patient is unknown. Two types of tests are being evaluated at the Environmental Health Center-Dallas. The first is in conjuction with AccuChem Laboratories. The second is intradermal challenge with mold toxins. A small series of patients have undergone intradermal challenge.

OUTLINE

Goals and objectives:

The goal is to learn generally about where mycotoxins are found and what systems they effect in the chemically sensitive individual.

Outline of talk/abstract

A. Signs and symptoms of mycotoxin exposure in the chemically sensitive

B. Use in foods

C. Types found in air and food

D. How they exacerbate the chemically sensitive

E. How diagnosed

F. How treated

Conclusion of what is to be learned:

The varied locations and responses to mycotoxins.

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A**Environmental Influence on the Autonomic Nervous System and the Effects on Endocrine Physiology**@

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Environmental factors that alter the circadian production of melatonin by the pineal gland, a neural structure that is an end organ of the sympathetic nervous system, markedly change the antioxidative defense capacity of aerobic organisms such as the human. The impact of the autonomic nervous system on the 24-hr rhythm is pineal melatonin production and secretion is well documented. The major environmental factors of concern in terms of their effects on the autonomic nervous system are the light/dark environment and stress. Both of these factors can influence either the amount of melatonin produced and/or the phasing of the circadian melatonin rhythm. The changes in melatonin induced by these environmental factors are very important because, as recently discovered, melatonin is a potent antioxidant. In particular, melatonin has been shown to specifically and efficiently scavenge the highly toxic hydroxyl radical (OH^-). Compared to other well-known antioxidants, e.g., vitamin E, glutathione, and mannito, melatonin is 10-1, 000X more efficient as a free radical scavenger. This being the case, any environmental factor that changes, especially reduces (which unfortunately light does), the amount of melatonin formed significantly also reduces the antioxidant capacity of the body. Also, any environmental factor, e.g., stress, that increases free radical production is likewise deleterious to cellular and organismal physiology. These findings are applicable to many free radical-related diseases, e.g., Parkinsonism, Alzheimer-s disease, cataractogenesis, oncogenesis, etc., as well as to the normal processes of aging.

OUTLINE

Goals and objectives:

To bring the audience up-to-date in reference ot the environmental control of pineal melatonin production and secretion.

To introduce the new data showing that melatonin is the most efficient free radical scavenger discovered to date.

To demonstrate how environmental factors that alter the melatonin rhythm also change the antioxidative capacity of the organism.

To illustrate how this relates to many disease states.

Outline of talk/abstract:

I. Introduction

A. Pineal gland and melatonin

B. Control of circadian melatonin rhythm

II. Functional significance of melatonin

A. As a time-giving hormone

B. As an antioxidant

C. Its relationship to specific disease states

III. Utility of melatonin in clinical medicine

Conclusion of what is to be learned:

The pineal hormone melatonin is a vitally important constituent in the body for many reasons, most importantly, because of its recently discovered antioxidant function.

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AOccurrence of Mycotoxins in Foods and Feeds@

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Mycotoxins occur in various commodities following appropriate conditions. The presence of a contaminating mold capable of producing one or more toxins is insufficient evidence for declaring a commodity or food contaminated with a mycotoxin. The specific mycotoxin must be demonstrated in the matrix before it can be claimed as contaminated with a mycotoxin. Even then the mere presence of a mycotoxin is not always evidence that it was or would be the cause of an intoxication. The conditions or

factors affecting mycotoxin occurrence include biological, environmental, and mechanical, as well as storage and processing. Therefore, foods and feeds can be contaminated with mycotoxins before harvest and during storage. Aflatoxins are most notable as contaminants of foods and ffeds as they have been subjected to greater scrutiny than most other mycotoxins. Among the other mycotoxins of interest regarding their occurrence in foods and feeds are certain trichothecenes, including deoxynivalenol, ochratoxin A., zearalenone, and fumonisisns. Combinations of mycotoxins may be important to consider in health problems because they do occur simultaneously in various matrices and many fungi are capable of producing more than one mycotoxin. Most countries have regulations regarding acceptable levels of specific mycotoxins in foods and feeds and the United States is no exception as there are guidelines established for aflatoxins and deoxynivalenol.

OUTLINE

Goals and objectives:

1. To discuss the meaning of mycotoxin occurrence.

2. To introduce the factors responsible for mycotoxin occurrence.

3. To discuss the occurrence of specific mycotoxins in feeds and foods.

Outline of talk/abstract:

I. Introduction

A. Meaning of mycotoxin occurrence

1. Producing fungus

2. Specific mycotoxin analyzed

(a) Problems of analysisCcommodity (matrix), mycotoxin suspected, available kits (quantititative or screening)

II. Factors Affecting Mycotoxin Occurrence

A. Biological

B. Environmental

C. Mechanical

D. Storage

E. Processing

III. Occurrence of Aflatoxins in Feeds and Foods

A. Raw products

B. Processed foods

IV. Occurrence of Trichothecenes in Feeds and Foods

A. Deoxynivalenol

B. Other trichothecenes

V. Occurrence of Ochratoxins in Feeds and Foods

A. Raw products

B. Foodstuffs

VI. Occurrence of Zearalenone in Feeds and Foods

VII. Occurrence of Fumonisins in Corn

VIII.Some Specific Problems Arising from Mycotoxin-Contaminated Feeds and Foods

A. Combinations of mycotoxins

IX. Regulations Involving Mycotoxin Occurrence in Feeds and Foods

Conclusions of what is to be learned:

> Mycotoxins occur in foods and feeds before harvest when conditions are appropriate for the fungi to invade the crop and grow.

Mycotoxins can occur in foods and feeds that are improperly stored.

Some imported foods are contaminated with mycotoxins.

The major concerns are the aflatoxins, certain trichothecenes, ochratoxin A, zearalenone, and fumonisins.

Governments do regulate the occurrence of some mycotoxins in foods and feeds.

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AExperimental Evidence for Mycotoxin-Induced Immunomodulation@

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A major economic effect of the mycotoxins is immuno-suppression, and the major mycotoxins having this effect are aflatoxins, certain trichothecenes, and ochratoxin A. The immunosuppression may involve specific immunoglobulins or antibodies if the amount of mycotoxin consumed is sufficient; however, the major effects appear to involve cellular immune phenomena and nonspecific humoral factors involved in immunity. These mycotoxins cause thymic aplasia, inhibit phagocytosis by macrophages, delayed cutaneous hypersensitivity, lymphocyte prliferation, and leukocyte migration. The involvement of the specific mycotoxins in infectious diseases is dependent upon the agent of disease, the toxin dose and constitution, animal species, and perhaps the sensitivity of the test. Gliotoxin, an immuno-suppressive compound, is produced by some pathogenic species of Aspergillus and may be involved in the pathogenesis of the disease. Embryonic exposure to certain mycotoxins may cause immunosuppressive effects in the offspring. Molecular approaches to the action of mycotoxins are necessary to understand their full impact as immunomodulators.

Goals and objectives:

A. To introduce certain mycotoxins as naturally occurring immunosuppressants.

B. To present experimental evidence for selected mycotoxins being immunosuppressive.

C. To provide for a discussion of the potential for mycotoxins to be involved as immunosuppressive agents in human disease.

Outline of talk:

I. IntroductionCintroduce subject of mycotoxins and which mycotoxins are considered important

in immunomodulation

II. Aflatoxins

A. Aflatoxins and antibody production

B. Aflatoxins and cell-mediated immunity

C. Aflatoxins and nonspecific humoral factors

D. Aflatoxins and infectious disease agents

III. Trichothecenes

A. Trichothecenes and antibody production, immunoglobulins, and nonspecific humoral factors

B. Trichothecenes and lymphocyte proliferation

C. Trichothecenes and other cellular responses

D. Trichothecenes and infectious disease agents

IV. Ochratoxin

A. Ochratoxin and humoral factors

B. Ochratoxin and cellular responses

V. Gliotoxin

A. Gliotoxin as an immunosuppressantCexperimental

B. Gliotoxin as a mycotoxin involved in an infectious disease processCa hypothesis

VI. Summary

Conclusions:

Natural toxicants must be considered as immunosuppressive agents.

Aflatoxins, some trichothecenes, ochratoxin A, and gliotoxin are considered as important immunomodulating mycotoxins.

The determination of the full potential of mycotoxins to be involved in immune disorders will be a

multidisciplinary effort.

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A**Improvement in Untreatable Cases with the Macrobiotic Diet, Nutrient and Hormone Corrections**@

Sherry A. Rogers, MD

Syracuse, NY

The total load has always incorporated looking at least for food, chemical, and mold sensitivities as well as nutrient and hormonal deficiencies.

Some unusual and highly resistent cases, many of which had also been to ecologists, responded

dramatically to the macrobiotic diet with nutrient and/or hormonal corrections. These include reversal of sarcoidosis, acute myelogenous leukemia, chronic fatigue of 12 years, pesticide poisonings, chemical sensitivities, chronic prostatitis, amblyopia, recurrent anaphylaxis, metastatic myeloma, and more.

This presentation stresses the importance of never losing sight of the total load, regardless of the improvement that the tools we are accustomed to using daily can bring about. It also stresses that, regardless of how seemingly hopeless a condition may be, the final cure seems to be limited only by our imaginations.

OUTLINE

Goals and objectives:

To show how the total load concept enables Aincurable@ conditions to clear.

Outline of talk/abstract:

Will show cases of chronic fatigue syndrome, sarcoidosis, seizures, retinal edema, acute myelogenous leukemia, and others that improve with attention to the total load of inhalant sensitivities, injections, environmental home controls for inhalants and chemicals, strict diet, correction of nutrient deficiencies as well as hormone deficiencies and more.

Conclusion of what is to be learned:

That Aincurable@ merely means that all of the above have not been done, for when they are, many impossible conditions improve or totally disappear.

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Over 300 references in my three-part article in *Intern Med World Rep* 1992.

A**Environmental and ECU Treatment of a Patient with Allergic Asthma, Laryngeal Stridor, and Chemical Sensitivities**@

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Dallas, TX

A 42-year-old nurse with intractable allergic asthma, laryngeal edema, and stridor spent six months in a conventional hospital, requiring intravenous epinephrine to control her asthma and stridor. Ingestion of any food induced stridor and she exhibited a spreading phenomenon of chemical sensitivity including

multiple medication reactions and intolerances.

She was transported by air 2,500 miles and admitted to the Environmental Control Unit (ECU) for stabilization and investigation.

By the use of the ECU and principles of the Environmental Medicine approach, her remarkable recovery will be outlined. This case and others illustrate the therapeutic efficacy of the ECU in the investigation and treatment of complex cases of allergy and sensitivity.

OUTLINE

Goals and objectives:

To help the audience become familiar with the use of the Environmental Control Unit in the treatment of complex allergies and sensitivities.

Conclusion of what is to be learned:

Illustrate the treatment methods available for complex allergies and sensitivities, and demonstrate some of the hazards and side effects of medication usage.

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AThe Environmental Control Unit (ECU) in the Diagnosis of Multiple Chemical Sensitivities.@ (Part 1) and ARecurrent Findings of Abnormal SPECT Scans in Chemically Sensitive Patients@ (Part II), at Multiple Chemical Sensitivity and its Relevance to Psychiatric Disease. (National Conference), Health and Welfare Canada, Chateau Laurier Hotel, Ottawa, Ontario, Canada. December 7, 1992.

A**Vitamin A: A Two-Edged Sword for the Fetus**@

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Vitamin A is an essential fat-soluble vitamin. Its importance in vision and maintenance of epithelium has been recognized for many years. In fact, the 13-cis form of retinoic acid is sometimes used to aid the treatment of intractable cystic acne. In livestock, many diseases are associated with the deficiency of

vitamin A, as often its precursors, the carotenes, are limited especially in winter. Without adequate vitamin A, low-grade disease usually ensues. In fact, because of compromised immune function, winter can be a fatal disease for wildlife and some livestock. Recent studies have shown that organochlorines released into the environment compound the picture, as they are responsible for accelerating the biotransformation and elimination of retinol (the stored form of vitamin A). Even in places of adequate vitamin A, retinol deficiencies have been recorded. Whether it is a deficiency of retinol or a direct effect of the organochlorine on development that causes disease, death, and developmental defects has not yet been determined. In any case the deficiency of vitamin A in places where adequate carotenes are present does indicate that probable exposure to manmade chemicals has occurred.

The fetus is as dependent on correct nutrition as the adult. Vitamin A is indeed a two-edged sword for the fetus, as too much is as harmful as too little. In a natural setting it is unlikely that too much vitamin A will be ingested by the pregnant adult (except through excessive liver intake) as the carotenes are limited in their conversion to retinol and retinoic acid. As vitamin A is a fat soluble vitamin, excessive supplementation can cause significantly elevated levels of the vitamin in tissues. Excessive vitamin A also causes birth defects via a mechanism of upsetting cell-cell adhesion and cell-cell recognition. Severe deformities have been reported following the administration of the active retinoid during pregnancy and in situations of known vitamin A deficiency.

OUTLINE

Goals and objectives:

To give the audience an understanding of the dichotomous nature of activity of vitamin A, to describe the metabolism and storage of the compound, and to describe the effects of excess and deficient states on the fetus.

Outline of talk/abstract:

The abstract first introduces the characteristic of the various forms of vitamin A, then describes the absorption, transport, metabolism and elimination of the retinoids, then outlines the biological activity of the carotenes and retinoids. Finally, deficiency and excess states are discussed with respect to the fetus.

Conclusion of what is to be learned:

The audience should learn that too much biologically available vitamin A is just as harmful as too little to the fetus and how excess exposure to organochlorines depletes vitamin A reserves.

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APrenatal Exposure: Is the Fetus at Risk in our Industrial Society?@

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It was not until the thalidomide disaster that it was recognized that environmental agents can cause harm to the fetus. In fact, before this time the public thought that all defective fetal development had a genetic cause. This incident showed that this was not so and sensitized the public to the hazards of exposing the developing embryo to foreign substances. Classical teratology (the study of birth defects) has involved examination of defective development in mammalian or avian species following exposure to specific chemicals or physical agents. The results the teratologist used to evaluate harmful effects included death of the embryo/fetus, intrauterine growth retardation, and structural defects.

Physiologically Based Pharmacokinetic Modeling is a process aimed at assessing the amount of a compound that reaches specific tissues in the fetus (or other parts of the body). Once this concentration of the absorbed dose is known then the latest thrust in teratology needs to be evaluated by looking at the biological effect of this dose on tissues. This latter task is undertaken using Biologically Based Dose Response Modeling, a process by which the effect of a dose of the compound or its metabolite on the fetus is evaluated. In addition, to these new ways of looking at chemicals on the devleoping fetus, this presentation will explore the broad concept of development.

Development used to be envisaged as events that occur only during the gestational period. With the recognition that numerous compounds affect neural development in children, the definition needs to be broadened. Development includes all organs in time and space that are responding through growth and differentiation to internal and external stimuli. For this reason the adult immune system and nervous system can be considered within the scope of development. If we do accept this definition of development, then the question needs to be answered: Is only looking at structural fetal development an adequate method of evaluating development?

OUTLINE

Goals and objectives:

To give an understanding of physiologically based pharmacokinetic (PBPK) and biologically based dose response (BBDR) modeling.

Outline of talk/abstract:

The abstract gives an overview to the predicament of the fetus with respect to exposure. Models (PBPK and BBDR) are described and the phenomenon of chemical trapping explained.

Conclusion of what is to be learned:

The audience will become aware of PBPK and BBDR models.

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A**The Influence of Chlorinated Hydrocarbons on Cellular Immune Parameters in Patients with Allergies and Chemical Sensitivities**@

Klaus D. Runow, MD, Karlheinz Schmidt, MD, PhD, Wolfgang Bayer, PhD, and Klaus M. Weber, MD

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Institute for Environmental Disease

Bad Emstal, Germany

The increasing problem of indoor air pollution as well as the increasing number of patients with allergies made us examine the influence of chlorinated hydrocarbons on cellular immune parameters. The human immune system is a highly sensitive indicator for toxic substances that stress the patient. It is known that heavy metals such as lead and mercury have an influence on the function of the T-suppressor-lymphocytes andCin the long run and in higher concentrationsCcan influence the whole immune system.

In research for more details we examined 52 patients, who suffer from chronic allergies respective from hypersensitivity. Here we had a closer look on 42 chlorinated hydrocarbons. The analysis of the toxic agents brought the following results: in many cases there was no evidence for Cyclodienes (such as Endrine, Aldrine, Dieldrin, and Lindane). It could be that these chemicals are too lipophile and that only minimum quantities dissolve in the blood so that it is impossible to measure them under the given circumstances. On the other hand, it might be possible that they are metabolized in the body to substances that we don=t know yet. Another possibilityCas we see it in the HexachlorepoxideCis that these substances are more likely to be found in the urine due to their polarity. The analysis of chemical solvents showed only slightly increased values referring to US-average values, whereas mainly Toluene, Benzene, Trimethylbenzene, and 1,1,1,-Trichlorethane could be measured. On the other hand, the values of Hexachlorobenzene, Polychlorinated Biphenyls, and Pentachlorophenol were remarkably increased. We can state that the natural killer cells and the suppressor T-cells are sensitive to chlorinated hydrocarbons. With the decrease of the number of NK-Cells the cellular immune reaction to bacterias, viruses, and tumor cells is reduced. Besides infections, the risk of cancer might be increased. By the decrease of the suppressor cells, the T_4/T_8-ratio increasesCa sign for an overreaction of the immune system, such as allergies and pseudoallergies.

OUTLINE

Goals and objectives:

Part of the diagnostic program in patients with allergies and chemical sensitivities should be:

1. Determination of chlorinated hydrocarbons;

2. Determination of cellular immune parameters.

Outline of talk/abstract:

Values of Hexachlorbenzene, Polychlorinated Biphenyls, and pentachlorophenol are remarkably high in Germany. HCB can be seen as the AGerman Marker.@

Conclusion of what is to be learned:

Natural-Killer-Cells (NK-Cells) and Suppressor T-Cells are sensitive to chlorinated hydrocarbons. With the decrease of the number of NK-Cells, the cellular immune reaction to bacterias, viruses, and tumor cells is reduced. Besides, the risk of cancer might be increased. By the decrease of T-Suppressor Cells the T_4/T_8-ratio increases, a sign for an overreaction of the immune system.

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Dr. K.-D. Runow, Inst. F. Environm. Diseases, Bad Emstal, Germany.

Prof. Dr. Dr. Karlheinz Schmidt, University of Tuebingen, Germany.

AImmunotoxic MechanismsCSensitive Indicators of Environmental Stress Load@

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Tuebingen, Germany

The immune system plays an important role in the interaction between the outside and the inside world of a living organismCespecially because it is linked to other systems such as the hormone system and the vascular system. Sensitivity and the ability of reaction necessarily belong to such a system, which works as a defense device of the individuum.

This sensitivity and reaction, on the other hand, imply that the immune system is susceptible to mechanical, thermic, radiological, chemical, and biological agents. These immunotoxic attacks are especially destructive if important cellular functions are damaged or even impossible as we see in patients with an HIV-infection, where the helper cells are affected. Also less specific agents can have immunotoxic

consequences and are in this way a helath risk.

Secondary immune deficiencies are also known especially as a result of narcotic users that have similar effects as quite a few environmental toxic agents. Particularly, interactions with membrane structures have been suspicious to be the toxic mechanisms. These interactions can influence important processes, which are important for the immune competence such as chemotaxis, adhesion, receptor-expression, proliferation, phagocytosis, killing, and so forth. In this way, they can cause an immune deficiency. On the other hand, these functions are important indicators for the dimensions of the environmental stress load (total body load).

A**Safety in Number? Too Little Too Late**@

Douglas B. Seba, PhD

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Environmental medicine professionals have been labeled for decades as being alarmists, uninformed, misguided, unscientific, and anti-progressive when it comes to chemicals, radiation, and other environmental factors. Actually, these environmentalists are simply pro the optimal conditions for human life. It is interesting then to see how many exposure standards have been lowered after being assured that the original level was perfectly safe.

Silicone breast implants recalled after 30 years; after 15 years of warning, the ozone hole has spread to both poles and losses occur year round; Parathion pesticide, registered in 1948, is now banned from 81 fruits, vegetables, and nuts; the lead standard was 30 micrograms/deciliter blood in the 70s, 25 in the 80s, and now 10 in the 90s, studies 50 years later on Japanese nuclear bombing survivors show much higher rates of cancer than predicted; and after 100 years, the hazards of electromagnetic exposure are finally beting documented.

With regard to particular effects on the autonomic nervous system theme of this conference, it is now reported that PCBs in the blood of pregnant women from occasionally eating tainted fish led to offspring with abnormal reflexes that have lasted at least four years. Food surveys used to set pesticide exposure levels include very few infants, pregnant women, or nursing mothers. Children of smoking mothers have twice the rate of extreme behavior problems. PCBs, dioxins, pesticides, plasticizers, etc. behave like hormones in mammals leading to impaired reproduction and immune suppression. Now the National Academy of Sciences laments how little is known about long-term exposure to low levels of chemicals on the central nervous system.

In sum, the initial exposure standards often decrease with time. The environmentalists were right all along.

OUTLINE

Goals and objectives:

The objective is to communicate the enormous number of exposure standards, initially thought to be safe,

that have been lowered when subsequent harm was discovered.

Outline of talk/abstract:

Talk will review numerous examples of exposure standard failures in the physical, chemical, and biological realms.

Conclusion of what is to be learned:

The conclusion is that exposure standards set by conventional methodologies are likely to cause harm unless the principles of environmental medicine are incorporated at the outset.

REFERENCES

Aprpoximately thirty references fromt he popular and scientific literature are available.

A**Breast Implants, Solvents, and Neurotoxic Exposure Can Be Related to Scintigraphic Abnormalities**@

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Cynthia E. Fincher, MS, PhD candidate

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Alcon

Dallas, TX

Earlier work relating diffuse focal defects in drug abusers was extended to clinically toxic patients who had implanted breast prostheses, who were exposed to organic solvents and pesticides, and who were exposed to nonspecific agents. These groups were compared to a group of age- and sex-matched subjects who were independently found to be normal from both a psychological and medical standpoint.

All subjects were given a two-phase brain scintigraphic study to relate regional cerebral blood flow to brain function. Minimental test results did not vary among the groups. Data were qualitatively and quantitatively assessed. The breast implant group showed a mild neurotoxic pattern in 14 of 20 (70%) and a single moderate (5%) and severe (5%) pattern. The pesticide group had the same extent of involvement: 12 of 15 (80%) with slightly more prominent disease (33% moderately affected). The group of 32 with organic solvent exposure was affected to the greatetest degree: 31%, severe; 22%, moderate; and 19%, mild. As expected, the 57 patients weith nonspecific exposure were affected over a wide range: 42% mild, 26% moderate, and 7% severe).

This pattern of widely disseminated focal abnormalities, often with mismatched flow and function, differed from that of chronic fatigue syndrome, which has a higher incidence of temporal lobe abnormalities and from both depression and schizophrenia, which often preferentially affect the frontal lobes.

The scintigraphic brain examination thus identified objective abnormalities in 76% of 124 subjects exposed to chemicals believed to compromise patients clinically. The abnormalities differ from chronic fatigue syndrome and from both affective and schizophrenic processes. The pattern is similar to that seen after exposure to neurotoxic agents of abuse such as cocaine and alcohol.

OUTLINE

Goals and objectives:

This presentation seeks to familiarize health care providers with developments in brain scintigraphy that can aid in the management of patients with environmentally related illnesses.

Outline of talk/abstract:

This presentation begins with a review of the techniques used in brain scintigraphy. The implications for environmental diseases are then explained by tracing recent work in psychiatric disease, chronic fatigue syndrome, drug abuse, and neurotoxicity. The effect of follow-up after therapy will then be illustrated along with our experience in caring for these patients. Objective data comparing normal controls, putative normal subjects, and afflicted individuals will then be compared using a statistical model derived from Dr. Kettlehut=s analyses. The implications for effective and efficient patient care will finally be discussed.

Conclusion of what is to be learned:

This presentation will acquaint health care providers with the advantages of using brain scintigraphy as an objective marker of enivornmentally induced disease and as a means of tracking the effect of clinical intervention.

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Simon, T.R., et al. 1992. Breast implants and organic solvent exposure can be associated with abnormal cerebral SPECT studies in Clinically impaired patients. *Radiology* 185(P):234. Radiological Society of North America.

A**Electrical Environmental Influences on theAutonomic Nervous System**@

Cyril W. Smith, PhD

Salford University

Salford, England

Electrically hypersensitive patients tend to present the same symptoms on electrical challenge as they do on challenge with environmental pollutants. The autonomic nervous system appears to be affected by pollutant injury and hence suspect in matters electrical.

Symptoms associated with the stimulation of the autonomic nervous system, both sympathetic and parasympathetic, will be correlated with the symptoms following electrical challenge in a controlled environment covering a wide range of frequencies at low intensity. Possible mechanisms for these effects and particularly those of frequency will be discussed in terms of autonomic pathways.

The autonomic nervous system is controlled by the hypothalamus both through direct descending neural pathways and through the endocrine system as discussed in 1992. These systems are not necessarily independent. The hypothalamus remains under the regulatory influence of the cortex and the limbic system which includes the hippocampus and olfactory and other areas. The hippocampus, which has its own definite electrical activity and sensitivity, has a neural connection to the hypothalamus, which in turn has a portal connection to the pituitary. The pineal is innervated by sympathetic nerve fibers and is also known to be affected by weak magnetic and electromagnetic fields and light.

OUTLINE

Goals and objectives:

To develop an appreciation of the influence of the electromagnetic or electrical environment on the normal and abnormal functioning of the autonomic nervous system both healthy and when impaired by environmental pollution effects.

Present overview of the electrical aspects of the autonomic nervous system.

Demonstrate involvement of specific frequencies with specific autonomic nervous system functions from clinical tests on electrically hypersensitive patients.

Conclusion of what is to be learned:

The electrical aspects of the autonomic nervous system and the ways in which it can be influenced by the electrical environment.

The way that specific frequencies can affect specific autonomic nervous system functions while other frequencies can therapeutically re-stabilize the autonomic nervous system.

The relation between pollutant and electrical stimulation of the autonomic nervous system.

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Smith, C.W. Feb. 27CMar. 1, 1992. Electromagnetic fields and the endocrine system. 10th Intl. Symp. *Man and His Environment in Health and Disease*. Dallas, TX.

A**Mold Allergy in China**@

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China owns a territory about 9.6 million square kilometers with a similar latitude as in America. The land raises high in the Northwest and slopes downward to the Southesast. Molds are favorite to grow not only for its subtropic temperature and mild humidity but also for the vast farmland and various crop cultivation that yield tremendous mold growing. Chinese dietary habits and lifestyle also create frequent mold contact either through inhalation or ingestion. Airborne mold surveys reveal there are two peaks of spore spreading, which occur in late spring and early autumn in Sourtheast China, while in Northwest China only one peak is present in late summer. Recently, some occupational mold allergies were encountered in China with mushroom clutivation, biological insecticidal powder manufacturing and Adenosine triphosphate production. An airborne allergenic mold survey in nationwide scale has been carried out since 1991. A book, *China Allergenic Aeromycology*, was newly published. It illustrated 100 different airborne molds with vivid scanning electormicroscopic pictures.

OUTLINE

Goals and objectives:

A general introduction of mold survey and correlates in its various clinical significance in China.

Outline of talk/abstract:

I. General trends of mold growth in China with geological, seasonal differences.

II. Lifestyle in China is relevant to mold allergy.

III. Three newly recognized molds induced occupational allergic alveolitis in China.

IV. Introduce some simple methods in detoxification of mycotoxins.

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